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Thromboembolic Complications After Surgical Correction of Mitral Regurgitation

Incidence, Predictors, and Clinical Implications

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Objectives We sought to define thromboembolic risk after surgery for mitral regurgitation (MR), particularly ischemic stroke (IS) compared with the general population.

Background Guidelines recommend surgery in asymptomatic patients with MR, but IS risks are unknown.

Methods In 1,344 patients (age 65 ± 12 years) consecutively operated for MR (procedures: 897 mitral valve repair [MRep] and 447 valve replacement: 231 mechanical mitral valve replacement [MVRm], 216 biological mitral valve replacement [MVRb]), thromboembolic complications, particularly IS (diagnosed by neurologists), during follow-up were assessed early (<30 days), midterm (30 to 180 days), and long-term (≥180 days).

Results Ischemic stroke occurred in 130 patients: 1.9 ± 0.4% and 2.7 ± 0.5% at 30 days and 180 days, respectively, and 8.1 ± 0.8% at 5 years. We found that IS rates were lowest after MRep versus MVRb and MVRm (6.1 ± 0.9% vs. 8 ± 2.1%, and 16.1 ± 2.7% at 5 years, respectively, $p < 0.001$). Comparison with population-expected IS showed high risk at <30 days (risk ratio 41, 95% confidence interval 26 to 60, $p < 0.001$ but $p > 0.10$ between procedures) and moderate risk at >30 days (risk ratio 1.7 overall; 1.3 for MRep; 0.98 for MVRb; 4.8 for MVRm). Beyond 180 days, IS risk declined further and was similar to the population for MRep (relative risk 1.2) and for MVRb (relative risk 0.9). Bleeding risk >30 days was lowest in MRep versus MVRb and MVRm (10-year risk 7 ± 1%, 14 ± 4%, and 16 ± 3%, respectively).

Conclusions Thromboembolic complications after MR surgery are a reason for both concern and encouragement. The risk of IS is notable early, irrespective of procedure, but in the long term it is not greater than in the population after MRep and MVRb. Preference for MRep should be emphasized, and trials aiming at preventing IS should be conducted to reduce thromboembolic and hemorrhagic risk after surgery for MR. (J Am Coll Cardiol 2008;51: 1203–11) © 2008 by the American College of Cardiology Foundation

Thromboembolic events (TEs) are serious complications of cardiac surgery (1). Most TEs are cerebrovascular (2), with the most serious, ischemic stroke (IS), resulting in poor quality of life and excess mortality (1,3–5). The incidence of IS early after cardiac surgery was reported mostly after coronary artery bypass grafting (CABG) surgery between 1% and 8% (1,4–7), but is less known after valve surgery (8,9), particularly for mitral regurgitation (MR) (10,11). A TE that occurs after MR surgery is important because 1) MR is frequent with aging (12); 2) mitral valve repair (MRep) is preferred for surgical treatment of MR so that previous data following valve replacement may not be relevant (13,14); and 3) surgery has been advocated for asymptomatic patients (15), in whom any complication represents serious concern. It is thus unclear whether TE risk is high in any surgery (14) or negligible with MRep (16), making anticoagulation unnecessary, or whether surgery multiplies spontaneous risk of stroke (17) in elderly patients with MR, a fact that may affect the new liberal indications for surgery in such patients. Resolving this question is difficult because with decreased rheumatic disease, older patients with MR (12) who are referred to surgery incur spontaneously a greater risk of stroke. There-

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Abbreviations and Acronyms

AF = atrial fibrillation
CABG = coronary artery bypass grafting
ICH = intracranial hemorrhage
IS = ischemic stroke
MR = mitral regurgitation
MRep = mitral valve repair
MVR = mitral valve replacement
RR = risk ratio
TE = thromboembolic event
TIA = transient ischemic attack

fore, it is essential to assess absolute TE risk but also to compare not only observed risk with that expected in the general population (18), but also early and late post-operative TE risk associated with MRep and mitral valve replacement (MVR). These comparisons will determine whether the survival advantage associated with MRep (19,20) is additive to lower embolic rates throughout follow-up. Thus, we examined the TE risk associated with various modalities of surgical correction of MR, particularly comparing IS risk to that expected in the population.

Methods

The present study was based on the consecutive experience of our institution (Mayo Clinic, Rochester, Minnesota) regarding outcome of MR surgery.

Study subjects. Inclusion criteria were as follows: 1) mitral surgery (repair or replacement) at our institution between January 1, 1980, and December 31, 1995; and 2) indicated for MR pure (no stenosis) and isolated (no aortic or tricuspid disease more than trivial). Exclusion criteria were presence of mitral stenosis, congenital or pericardial disease, previous mitral valve surgery, and previous or simultaneous aortic or tricuspid valve replacement (tricuspid repair was not an exclusion criteria). Patients with associated CABG were not excluded.

Clinical practice and definitions. Baseline characteristics and comorbidity were recorded as noted by a patient's personal physician at our institution. pre-operative echocardiographic data were prospectively measured for patient evaluation and collected for this study by electronic download without alteration. Mitral repair was guided by the surgeon's assessment of lesions (21), and replacement was performed if repair was impossible. Choice of mechanical or biological prosthesis was based on discussion between patient and surgeon. Preservation of posterior leaflet chordae was systematic, and specific surgical details (anterior leaflet chordae, foramen ovale, atrial closure) varied according to surgeon's decisions. Post-operatively, the use of heparin followed by warfarin sodium was usual, but the intensity and duration of anticoagulation were determined by personal physicians according to anticoagulation guidelines. Treatment with warfarin sodium was recorded if administered >3 months post-operatively. Events were determined by review of medical records, hospital notes, questionnaires, and telephone calls to patients, families, and physicians. Complete follow-up was available for 1,321 (98.2%) patients. Neurological diagnoses were made by neurologists integrating all information available regarding neurological symptoms, examination at event, and during follow-up visits and neurovascular imaging. All neurological diagnoses were based on validated definitions (18,22–24). Ischemic stroke was persistent (>24 h) focal neurological deficit attributed to altered circulation of cerebral hemispheres, brain stem, or cerebellum. Computed tomography or magnetic resonance during an acute episode were not indispensable to neurological diagnosis (obtained in 125 of 201 patients, 62% with IS or transient ischemic attack [TIA]) (18,24). A TIA was a focal neurologic event of complete and rapid resolution (<24 h) related to altered brain circulation (23,24). Peripheral embolic event was defined by operative, autopsy, or clinical documentation of embolism causing peripheral (noncerebral) arterial obstruction (24). Bleeding event was internal or external bleeding causing death, hospitalization, or permanent injury or requiring transfusion (24). Intracranial hemorrhage (ICH) was diagnosed with the use of imaging or autopsy. Atrial fibrillation was diagnosed with the use of electrocardiogram.

Statistical analysis. Baseline characteristics are presented as mean ± SD for continuous variables. Group comparisons used a standard *t* test or chi-square test as appropriate. First-event rates were estimated with the Kaplan-Meier method censoring after the first event or at end of follow-up, and multiple events were accounted for by yearly linearized rates, all expressed in percent per year ± SE (24). Absolute hazards of embolisms were examined and periods of high, medium, and low risk were defined based on inflections of the time-hazard curves. First event rates were compared between groups using the 2-sample log-rank test and with expected rates in an Olmsted County population (matching for gender, age, and rhythm from the Rochester, Minnesota Stroke Registry) by using the 1-sample log-rank test. Logistic regression was used to predict first events at specific intervals (30 and 180 days) after surgery. Cox proportional hazards modeling was used to define long-term first events' predictors. Variables with $p < 0.10$ by univariate analysis were candidate predictors in multivariate models, and $p < 0.05$ was significant.

Results

Baseline characteristics. During the study, 1,344 patients had surgery for MR, MRep in 897 (67%), mechanical mitral valve replacement (MVRm) in 231 (17%), and biological mitral valve replacement (MVRb) in 216 patients (16%). Reoperation was performed in 133 patients during follow-up. Mitral regurgitation etiology was myxomatous valve in 856, ischemia in 261, endocarditis in 76, rheumatic fever in 86, and miscellaneous in 65 patients. Bioprostheses were Carpentier-Edwards (Edwards LLC, Irvine, California) in 159, Ionescu-Shiley in 43, Hancock in 11, and Medtronic Intact (Medtronic Inc., Minneapolis, Minnesota) in 3 patients. Mechanical prostheses were Starr-Edwards (Edwards LLC) in 143, St. Jude (St. Jude Corp., St. Paul,

Table 1 Baseline, Operative, and Post-Operative Characteristics

Population Variables	Overall (n = 1,344)	MRep (n = 897)	MVRm (n = 231)	MVRb (n = 216)	p Value
Pre-operative clinical characteristics					
Age, yrs	65 ± 12	65 ± 12	60 ± 11	70 ± 11	<0.0001
Male gender, %	61	64	62	48	<0.0001
Hypertension, %	36	37	29	39	0.03
Diabetes, %	10	8	11	13	0.07
Creatinine, mg/dl	1.4 ± 0.6	1.4 ± 0.7	1.3 ± 0.6	1.3 ± 0.4	0.92
Organic MR, %	81	83	80	69	<0.0001
AF, %	41	37	51	44	0.0006
NYHA functional class III to IV, %	57	48	69	78	<0.0001
Pre-operative echocardiographic characteristics					
EF, %	58 ± 13	59 ± 12	56 ± 14	56 ± 14	0.02
LVD, mm	61 ± 9	61 ± 9	61 ± 9	61 ± 9	0.91
LVS, mm	39 ± 12	39 ± 13	39 ± 10	39 ± 10	0.97
LAD, mm	54 ± 10	54 ± 9	54 ± 10	54 ± 11	0.85
Operative and post-operative characteristics					
Bypass time	98 ± 48	90 ± 47	110 ± 49	118 ± 50	<0.0001
CABG, %	38	38	33	43	0.13
Warfarin sodium therapy, %	51	41	95	44	<0.0001
Patients with thromboembolic complications, n (%)*					
Ischemic stroke	130 (10%)	65 (7%)	44 (19%)	21 (10%)	
TIA	81 (6%)	50 (6%)	21 (9%)	10 (5%)	
Peripheral TE	21 (1.6%)	11 (1.2%)	6 (2.6%)	4 (1.9%)	
Any TE	212 (16%)	114 (13%)	64 (28%)	34 (16%)	

*n indicates the number of patients with the complication, and the percentages are calculated as the ratio of n with the listed thromboembolic complications during follow-up for each group by the total number of patients in the series or group.

AF = atrial fibrillation; CABG = coronary artery bypass graft; EF = ejection fraction; LAD = left atrial diameter; LVD = left ventricular diameter; LVS = left ventricular end-diastolic and end-systolic diameter; MR = mitral regurgitation; MRep = mitral valve repair; MVRb = mitral valve replacement biological; MVRm = mitral valve replacement mechanical; NYHA = New York Heart Association; TE = thromboembolic event; TIA = transient ischemic attack.

Minnesota) in 59, Bjork-Shiley in 27, and Hall-Medtronic (Medtronic Inc.) in 2 patients. We performed CABG in 507 patients. The pre-operative characteristics summarized in Table 1 show differences between MRep, MVRm, and MVRb, particularly for age. Atrial fibrillation (AF) was present pre-operatively in 544 patients (Table 1), and 168 patients developed AF during follow-up. Warfarin sodium treatment was prescribed after surgery for 51% of patients (95% with MVRm who survived to receive permanent anticoagulation). Patients with TE are also listed in Table 1 overall and by surgical procedure.

IS after MR surgery. We found that IS occurred in 130 patients (most frequent TE, Table 1) with full resolution of IS manifestations in only 23 (18%). The incidence of IS was 1.9 ± 0.4% (30-day), 2.7 ± 0.5% (180-day), and 8.1 ± 0.8% (5-year follow-up) in excess of expected rate for this population ($p < 0.0001$). Linearized rate of first IS was 1.5 ± 0.1 per 100 patient-years (Table 2), and when accounting for 29 recurrent IS, was 1.75 ± 0.1 per 100 patient-years. However, marked rate changes were noted over time. Table 2 shows contrasting high early linearized rates; while most events occurred later, there were higher long-term IS rates after MVRm than after other corrections ($p < 0.0001$) (Fig. 1). Within the first 30 days, IS incidence was greater after MVRb (4.6 ± 1.5%) than MRep (1.5 ± 0.4%) or MVRm (1.3 ± 0.8%, $p < 0.0001$). Up to 180 days, MRep showed the lowest IS incidence versus MVRm and MVRb. After 180 days, IS rates were lowest after MRep and MVRb versus MVRm (Table 2). There was no significant difference in stroke rates between the 30- to 90-day follow-up and the 90- to 180-day follow-up.

A comparison of IS observed versus expected in Olmsted County population with similar characteristics, particularly age, is presented in Table 3. For all patients and all times, observed-to-expected IS risk ratio (RR) is 2.1 (doubling of spontaneous risk), but with marked time and procedure heterogeneity. Indeed, excess risk versus expected is very high at <30 days (RR 41, similar for all procedures) but declines to 1.7 thereafter. The pattern of early high risk declining long term is similar with MRep and MVRb, with similar IS risk ratios to expected (1.6 vs. 1.7). For MRep and MVRb, >180 days IS risk returns to that of general population. However, for MRep, IS risk remains elevated at >30 days, up to 180 days. With MVRm excess IS risk is high, that is, 4 to 10 times normal throughout follow-up.

Predictors of IS. For IS <30 days, univariate predictors were age, female gender, intra-aortic balloon pump, coronary disease, hypertension, and MVRb (Table 4). Only female gender was weakly associated with early IS independently of age ($p = 0.047$). For IS at 30 days to 180 days, independent predictors were age, hypertension, and MVRm (Table 4). Beyond 6 months, univariate IS predictors were

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Table 2 Incidence of Ischemic Stroke Event After MR Surgery Overall and by Surgical Procedure and Post-Operative Phase

Group	Follow-Up			
	Entire	≤30 Days PO	30–180 Days PO	>180 Days PO
Overall	Events: 130 5 yrs: 8.1 ± 0.8% 10 yrs: 12.9 ± 1.2% 1.5 ± 0.1 %PY	Events: 25 30 days: 1.9 ± 0.4% 23.9 ± 4.8 %PY	Events: 10 180 days: 2.7 ± 0.4% 2.02 ± 0.6 %PY	Events: 95 1.2 ± 0.1 %PY
MRep	Events: 65 5 yrs: 6.1 ± 0.9% 10 yrs: 9.9 ± 1.3% 1.15 ± 0.1 %PY	Events: 13 30 days: 1.5 ± 0.4% 18.3 ± 5 %PY	Events: 5 180 days: 2.1 ± 0.5% 1.5 ± 0.6 %PY	Events: 47 0.9 ± 0.1 %PY
MVRm	Events: 44 5 yrs: 16.1 ± 2.7% 10 yrs: 23.3 ± 3.5 2.7 ± 0.4 %PY	Events: 3 30 days: 1.3 ± 0.8% 16.6 ± 9.6 %PY	Events: 4 180 days: 3.2 ± 1.2% 4.7 ± 2.3 %PY	Events: 37 2.5 ± 0.4 %PY
MVRb	Events: 21 5 yrs: 8.0 ± 2.1% 10 yrs: 12.2 ± 2.9% 1.65 ± 0.4 %PY	Events: 9 30 days: 4.6 ± 1.5% 60 ± 20 %PY	Events: 1 180 days: 5.2 ± 1.6% 1.5 ± 1.5 %PY	Events: 11 0.9 ± 0.3 %PY

In each cell, "events" indicates the number of ischemic strokes for the period and procedure. Incidences of ischemic strokes are indicated with the time at which they are estimated and ± SE of the estimate; the last line indicates the yearly linearized rate (±SE) of ischemic strokes.
PO = post-operatively; %PY = per 100 patient-years; other abbreviations as in Table 1.

age, MVRm, AF at surgery or before the event, and left atrial dimension >50 mm. Independent IS predictors at >180 days were age and MVRm, whereas MRep was independently predictive of less-frequent IS (Table 4) (RR 0.5, 95% confidence interval [CI] 0.3 to 0.8). Although AF was not predictive overall of IS ($p > 0.10$), after exclusion of patients with MVRm, AF was, independently of age, associated with a greater stroke rate ($p = 0.05$; RR 1.4, 95% CI 1.01 to 3.8). A history of pre-operative stroke was not univariate ($p = 0.66$) or adjusted ($p = 0.69$) independently predictive of post-operative IS.

Incidence of ischemic stroke or TIA. Transient ischemic attack occurred in 81 patients, followed by IS in 10 and isolated in 71, and IS/TIA occurred in 201 patients (2.6 ± 0.5% at 30 days, 13.4 ± 1% and 20 ± 1% at 5 and 10 years). We found that IS/TIA was similar in MRep, MVRm, and MVRb at 30 days (2.4 ± 0.5%, 1.8 ± 0.9%, 4.6 ± 1.5%, $p > 0.10$) and 180 days (3.9 ± 0.6%, 4.1 ± 1%, 6.3 ± 1.7%, $p > 0.10$). At 5 years, IS/TIA was lowest in MRep, 10.9 ± 1.1% (2.0 ± 0.2% patient-years), which was not different from MVRb, which was 13.2 ± 2.6% (2.6 ± 0.5% patient-years), but lower than MVRm, which was 23.4 ± 3.1% ($p < 0.0001$, 4.1 ± 0.5% patient-years). Compared with expected IS/TIA in general population, at <30 days, excess risk was consistent (overall RR 43) regardless of procedure (Table 5). Beyond 30 days, risk remained significantly high versus expected, and although it decreased markedly over time in all groups, it remained considerable in MVRm beyond 180 days (RR 4.9) (Table 5).

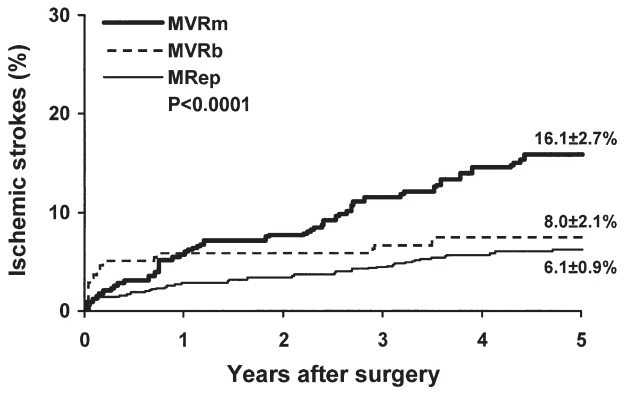

Figure 1 Incidence of First Ischemic Stroke After Surgery for Mitral Regurgitation

The numbers with each curve indicate the 5-year estimated rate of ischemic stroke ± SE. MRep = mitral valve repair; MVRb = mitral valve replacement biological; MVRm = mitral valve replacement mechanical.

ICH and total strokes (IS/ICH). Ten patients experienced ICH: 1 in MRep, 5 in MVRm, and 4 in MVRb. In addition, 1 patient had subarachnoid hemorrhage. Compared with population-expected ICH, MRep had low relative risk (0.17, 95% CI 0.0 to 0.97, $p = 0.04$) and MVRm had high relative risk (3.8, 95% CI 1.2 to 8.8, $p = 0.003$), whereas MVRb had notable relative risk (2.2, 95% CI 0.6 to 5.7) but did not reach statistical significance ($p = 0.12$). For IS or ICH stroke (140 patients), comparison with population-expected rates shows high relative risk with MVRm (5.2, 95% CI 3.8 to 6.9, $p < 0.0001$) both <30 days (39, 8.1 to 115, $p < 0.0001$) and after 30 days (4.9, 3.6 to 6.5). For MRep and MVRb, IS/ICH risk became similar to expected after 30 days.

All embolic events (IS, TIA, peripheral, and mesenteric embolism). Post-operatively, 212 patients experienced TE irrespective of location (Table 6). MRep had the lowest

Table 3 First Ischemic Stroke Risk After MR Surgery Expressed as Risk Ratio to Expected First Ischemic Stroke Rates in the Population

	Follow-Up				
Group	Entire	<30 Days PO	≥30 Days PO	30–180 Days PO	>180 Days PO
Overall series					
Risk ratio	2.1	41	1.7	2.9	1.6
95% CI	1.8–2.5	26–60	1.4–2.1	1.4–5.3	1.3–1.9
p value*	<0.001	<0.001			
MRep					
Risk ratio	1.6	31	1.3	2.1	1.2
95% CI	1.3–2.1	16–53	0.97–1.7	0.7–4.8	0.9–1.6
p value*	<0.001	<0.001			
MVRm					
Risk ratio	5.1	43	4.8	10.4	4.3
95% CI	3.7–6.9	9–126	3.4–6.5	2.8–27	3–5.9
p value*	<0.001	<0.001			
MVRb					
Risk ratio	1.7	72	0.98	1.5	0.9
95% CI	1.1–2.6	33–137	0.5–1.7	0.1–8.5	0.5–1.6
p value*	0.01	<0.001			

*p value applies to the comparison between observed and expected rates of first ischemic stroke.
CI = confidence interval; other abbreviations as in Table 1.

incidence at 11.6 ± 1.1% after 5 years (2.1 ± 0.2% patient-years), which is lower than MVRm (23.8 ± 3.1% [4.3 ± 0.5% patient years, $p < 0.001$]) but not different from MVRb (14.9 ± 2.8% [2.8 ± 0.5% patient-years, $p > 0.10$]), a difference sustained at 10 years (Fig. 2).

Incidence and predictors of bleeding. Bleeding occurred in 136 patients (58 MRep, 39 MVRm, and 39 MVRb), 51 at <30 days (3.9 ± 0.5%). Excluding these early bleedings, 5- and 10-year rates were 5 ± 1% and 10 ± 1%, respectively. Lower 10-year rates were observed with MRep (7 ± 1%, 0.7 ± 0.1% patient-years) versus MVRb (14 ± 4%, 1.7% patient-years) and MVRm (16 ± 3%, 3.4 ± 0.5% patient-years). Early (30-day) bleeding was only age-related ($p = 0.007$). Long-term bleeding independently increased with age (RR 1.14, 95% CI 1.02 to 1.27 per 5 years), male gender (1.65, 95% CI 1.04 to 2.7), and MVRm (2.5, 95% CI 1.5 to 3.9), and decreased with MRep (0.39, 95% CI 0.25 to 0.61). Patients justifying intention to treat by anticoagulation (AF or MVRm) incurred a higher bleeding rate independently of age (1.52, 95% CI 1.08 to 2.15, $p < 0.02$).

Table 4 Independent Predictors of First Ischemic Stroke After MR Surgery

Predictors	<30 Days PO OR, 95% CI p Value	30–180 Days PO OR, 95% CI	>180 Days PO RR, 95% CI
Female gender	2.3, 1.01–5.4 0.047		
Hypertension		4.3, 1.2–20	
MVRm		6.0, 1.4–25	3.0, 1.9–4.65
Age (per 5 yrs)		1.4, 1.0–2.3	1.1, 1.03–1.3
MRep			0.5, 0.3–0.8

OR = odds ratio (by logistic models); RR = risk ratio (by Cox proportional hazards survival models); other abbreviations as in Tables 1 and 2.

Discussion

The present study, which analyzes a large cohort of patients operated for MR for time dependence of TE events after surgery and compares IS rates to the general population, provides a unique view of TE events after MR surgery. Our observations are both concerning and encouraging. Concerns stem from excess risk of IS and of IS-TIA. Encouraging is the decline of TE events over time post-operatively, so that in MRep or MVRb, IS rates are not different in the long term from the general population. Thus, MRep, which compared with MVR results in the restoration of life expectancy, also has the advantage of imposing no excess IS risk after the sixth post-operative month and is confirmed as the preferred surgical correction of MR. Conversely, MVRm is associated, beyond the excess mortality previously noted, with sustained risk of IS and bleeding and is the least desirable correction of MR. Beyond these broad conclusions, it is important to examine detailed TE risk and how it can be minimized.

Early TEs. Previous research focused on thromboembolic events early after cardiac surgery, mostly after coronary bypass surgery (1,4–7). Early TE events directly causally linked to surgery are important. In our series, rates of IS or IS/TIA early after surgery (30 days) of 1.9% and 2.6% are lower than reported after coronary bypass (1,4,7). These rates are also lower than neurologic events after mitral surgery (3,11), particularly because of a strict neurological definition of IS or TIA (18), but are high enough to justify careful attention. Macroembolization is now rare, involving

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Table 5 Risk of the Combined End Point First IS-TIA After MR Surgery Compared With Expected First IS-TIA Rates in the Population

Group	Follow-Up				
	Entire	<30 Days PO	≥30 Days PO	30–180 Days PO	>180 Days PO
Overall series					
Risk ratio	2.7	43	2.3	4.7	2.0
95% CI	2.4–3.2	30–60	1.95–2.7	2.9–7.2	1.7–2.4
p value*	<0.001	<0.001			
MRep					
Risk ratio	2.2	39	1.8	4.2	1.6
95% CI	1.8–2.7	24–59	1.5–2.2	2.2–7.2	1.2–1.9
p value*	<0.001	<0.001			
MVRm					
Risk ratio	5.8	43	5.4	9.6	4.9
95% CI	4.4–7.4	11.6–109	4.1–7.0	3.1–22	3.7–6.5
p value*	<0.001	<0.001			
MVRb					
Risk ratio	2.2	57	1.6	3.7	1.4
95% CI	1.5–3.1	26–106	1.0–2.4	1.0–10.7	0.8–2.1
p value*	<0.001	<0.001			

*p values applies to the comparison between observed and expected rates of first IS-TIA.
IS-TIA = ischemic stroke-transient ischemic attack; other abbreviations as in Tables 1, 2, and 3.

thrombotic, fat, or gaseous emboli from extracorporeal circulation or aortic atherosclerosis (25–27). The risk of TE is not just procedural and remains high within 30 days (approximately 40× the risk of spontaneous IS). Prosthetic materials activate platelets with sustained platelet deposition (28) and clot formation. This observation justifies prevention of thrombus formation after MR surgery, irrespective of procedure (13,29). Higher early TE and IS risk in women is poorly explained, but coherent observations (9,30) underscore the need for prospective mechanistic studies addressing this excess risk.

Long-term thromboembolic and hemorrhagic complications. A clear result involves late complications of MVRm, which was unclear in previous studies. For MVRm, a clinical trial did not suggest excess stroke rate (14) but was contradicted by clinical practice studies showing high rates of TE (2,9,31,32). Our large long-term study emphasizes greater TE and IS rates with MVRm than MVRb (9) or MRep. Despite declining rates of IS over time, excess risk with MVRm is evident >6 months. Risk estimation is difficult due to younger age with MVRm versus MVRb, but comparison to the age-expected rate of IS or IS/TIA shows that MVRm multiplies long-term risk by 4 to 5. Also, in multivariate analysis, IS risk with MVRm is 3× greater versus MVRb. MVRm requires anticoagulation with a notable bleeding rate, >3% yearly, which is 2.5× higher versus MVRb. This combined inherent excess risk should be a renewed

Table 6 Incidence of Any Thromboembolic Event After MR Surgery Overall and by Surgical Procedure and PO Phase

Group	Follow-Up			
	Entire	≤30 Days PO	30–180 Days PO	>180 Days PO
Overall	5 yrs: 14.2 ± 1% 10 yrs: 20.7 ± 1.4% 2.6 ± 0.2 %PY	30 days: 2.9 ± 0.5% 38.6 ± 5.8 %PY	180 days: 4.7 ± 0.6% 4.7 ± 1 %PY	2 ± 0.1 %PY
MRep	5 yrs: 11.6 ± 1.1% 10 yrs: 17.2 ± 1.7% 2.1 ± 0.2 %PY	30 days: 2.5 ± 0.5% 31 ± 6.6 %PY	180 days: 4.2 ± 0.7% 4.2 ± 1.1 %PY	1.6 ± 0.2 %PY
MVRm	5 yrs: 23.8 ± 3.1% 10 yrs: 33.1 ± 3.8% 4.3 ± 0.5 %PY	30 days: 1.8 ± 0.9% 22.2 ± 11.1 %PY	180 days: 4.6 ± 1.4% 7.1 ± 2.9 %PY	3.9 ± 0.5 %PY
MVRb	5 yrs: 14.9 ± 2.8% 10 yrs: 20.8 ± 3.5% 2.8 ± 0.5 %PY	30 days: 5.7 ± 1.6% 73.5 ± 22.15 %PY	180 days: 7.4 ± 1.9% 4.5 ± 2.6 %PY	1.8 ± 0.4 %PY

In each cell, incidences of embolic events are indicated with the time at which they are estimated, ±1 SE of the estimate. The last line indicates the yearly linearized rate (±SE) of ischemic strokes.
Abbreviations as in Table 1.

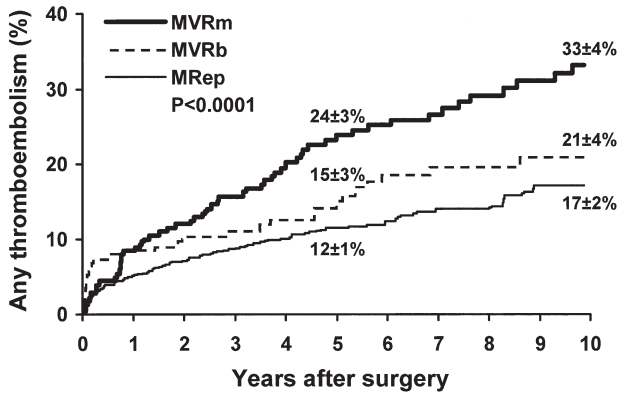

Figure 2 **Incidence of Any First TEs After Surgery for MR**

The numbers with each curve indicate the 5- and 10-year estimated rate of TEs ± SE. MR = mitral regurgitation; TE = thromboembolic event; other abbreviations as in Figure 1.

incentive to make all efforts to avoid MVRm for MR correction.

For MVRb and MRep, we also observed a marked risk decline >30 days. MRep was associated with the lowest absolute rate of TE, IS, and IS/TIA. This advantage of MRep was controversial (19,33,34), and age differences require comparison with expected rates. A remarkable result is that IS risk (the most frequent and serious TE complication) is similar >180 days in MVRb and MRep and not significantly elevated compared to the general population. Thus, MRep results in long-term restoration not only of life expectancy (35,36) but also of IS risk. MRep is also remarkable by providing the lowest bleeding risk and is unique in combining long-term morbidity to mortality benefit.

Clinical and preventive implications. Our study shows that, after MR surgery, immediate IS risk is close to 2% overall and slightly >1% for valve repair. This risk should, in our opinion, not discourage early surgery in asymptomatic patients, recently endorsed by guidelines (15), but should be made clear to patients considering MR surgery. For procedure choice, our data reinforce MRep preference for surgical correction of MR. The previously demonstrated MRep survival benefit (19) and lowest risk of embolism and hemorrhage concur in supporting this approach. The return of IS risk to that in the general population 6 months after MRep is particulary important in asymptomatic patients in whom a low rate of post-operative complications is essential to the operative decision. If repair is not possible, MVRb, with lower TE and hemorrhagic risk than MVRm, should be carefully considered.

Early IS risk is only transient, but strategies should be developed to lower it. A similar risk with MVRm versus MRep or MVRb may reflect more careful attention at anticoagulation. Effective anticoagulation assessment requires prospective evaluation, but our data clearly emphasize the need for effective anticoagulation. Other potential TE determinants and therapeutic interventions have been previously discussed. Antithrombotic medication, such as aspirin, have risks but also benefits (37) that should be evaluated. Atrial fibrillation is frequent after surgery and may contribute to TE (38). The association of diagnosed atrial fibrillation with IS or IS/TIA was weak overall but, excluding MVRm (with high TE risk irrespective of rhythm), AF predicted risk of IS, TE (relative risk 1.5, 95% CI 1.1 to 2.1, p = 0.002), and embolism or bleeding (1.4, 95% CI 1.1 to 1.7, p = 0.035). Although surgical AF prevention (39) and left atrial appendage closure (40) deserve further investigation, these findings suggest that AF is not benign in MR, justifying surgery after AF but also suggesting that early surgery in sinus rhythm may provide best outcome.

Beyond the initial high-risk 30-day phase, exact boundaries of intermediate risk are difficult to define. A comparison to expected IS risk provides new insights (29). Slow healing of mitral repair, which is up to 12 weeks (41) for complete endothelial restoration (42), may be linked to 30 to 180 days' TE risk. Whether prolonged anticoagulation after MRep would prevent IS and TIA during this intermediate phase is conjectural but should be considered because such finite anticoagulation represents modest bleeding risks. Chronically, IS risk of MRep is low and antithrombotic treatment should be individualized (37). In older patients with MVRb and faster endothelial restoration (43,44), no excess embolic risk is noted >30 days and prolonged anticoagulation is of dubious benefit (45).

High long-term TE-risk after MVRm despite anticoagulation is a concern. Frequent monitoring of anticoagulation was linked to low TE rates (46), and home self-monitoring, which now is widely applicable, appears beneficial in pilot trials (47) and is attractive in view of sustained high embolic and hemorrhagic risk in MVRm.

Study limitations. Different baseline characteristics between surgical procedures, particularly age, are expected. Beyond comparing absolute TE rates, adjusting for age in multivariate analysis and comparison to age-expected IS or IS/TIA risk accounted for these differences. The analysis of mid- and long-term post-operative phases (30 to 180 days and >180 days) carries the potential for bias because the censoring of early events (left-truncation) is justified by changing events hazards over time. Thus, interpretation of partial rates should be prudent and emphasizes the importance of comparison to expected risk (48). With change in TE hazard over time, quality criteria for anticoagulation are imperfectly defined. Thus, obtaining measures of compliance, regularity, and efficacy were not possible in our study. We could not measure how specific anticoagulation characteristics may be linked to embolic and hemorrhagic risks, and thus comprehensive community studies and clinical trials are necessary. However, by demonstrating excess risk incurred by patients undergoing MR surgery, candidates for clinical trials can be better defined. Conversely, long-term,

MRep and MVRb are not linked to excess IS risk, a reassuring observation.

Conclusions

This large study of MR surgery provides observations causing both concern and encouragment regarding post-operative TE events. Indeed, MR surgery is followed, versus the general population, by excess IS risk and IS/TIA risk. It is also concerning that, throughout, follow-up patients with MVRm incur a high risk of TE or bleeding. However, encouraging are the brisk decrease in TE rate after the early post-operative phase and the fact that, with MRep or MVRb, long-term IS rates are similar to the general population. Thus, MRep provides, in addition to its low mortality, the lowest morbidity and is confirmed as the preferred correction of MR. Conversely, MVRm shows sustained risk of IS and bleeding and is least desirable for MR correction. To support guideline recommendation of early MR surgery in asymptomatic patients, MRep performance is an essential condition, and clinical trials should be designed to minimize the risk of stroke after surgery.

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